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(54) Hard gelatin capsules resistant to denaturation and the production thereof

(57) Formulated hard gelatin capsules resistant to denaturation are described. The capsules contain 0.01 to 5 weight % of free radical scavenger for the whole amount of the content, whereby the decrease in solubility and the insolubilization can be prevented. The capsules still maintain stable drug releasing property.

EP 0 695 544 A1

Description

TECHNICAL FIELD

This invention relates to hard gelatin capsules resistant to denaturation which are not accompanied by decrease of the solubility or insolubilization time dependently and which release the drug therein steadily. This invention also relates to the production of said capsules.

PRIOR ART

Hard gelatin capsules which are formulated by packing some contents like drugs in capsule shells made of hard gelatin have widely been used for the improvement of drug handling. In the formulation of acid-susceptible drugs or sustained release preparations, tablets are not suitable because there is much difference in bioavailability among individuals who have taken them. The hard gelatin capsules have usually been utilized to avoid this problem.

For example, it is usual that a granulated drug is coated with an aqueous coating solution of enteric polymer or water-insoluble polymer and packed in hard gelatin capsules in order to minimize the difference in the rate of intestinal drug absorption among persons which depends on the velocity of drug movement in the gastrointestinal tract. Moreover, the formulation by hard gelatin capsules is also utilized to avoid the damage of appearance of drugs, which is sometimes accompanied by the addition of amphiphilic compounds, e.g., Tween (trade name), Span (trade name), polyethylene glycol (PEG), which are added to improve the wettable property of sparingly soluble drugs.

In the above cases, however, the hard gelatin capsules are sometimes denatured during storage under a warmed condition and the drug release is greatly inhibited since the capsules contain aqueous-coating granular drugs or amphiphilic compounds with polyoxyethylene chains.

The reason may be attributable to that PEG, triethyl citrate, etc. used as plasticizer in aqueous coating or the polyoxyethylene chain of the amphiphilic compounds is thermally decomposed to yield peroxidation products such as aldehydes, which act to induce intramolecular or intermolecular bridge formation or polymerization in gelatin.

To solve this problem, for example, organic solvents containing no plasticizer may be used in the coating step. This solution, however, is not desirable because there is a problem of residual solvent since the use of organic solvents is directed to be controlled in view of environmental pollution. In this situation, it is possible to use a plasticizer, e.g., triacetin, glycerol monostearate, which does not produce any peroxide, but they are not suitable because they are inferior in film formation, decomposed with acids to deteriorate acid resistance or drug release time dependently, and emit unpleasant odor, e.g. odor of acetic acid.

It is also known as an alternative method that a protein such as casein, soybean protein, skim milk or collagen is added as an additive to capsules (Japanese Kokai Publication Sho-51-15094). The method, however, is insufficient for inhibiting the generation of peroxides; in order to obtain the desired effect, it is necessary to increase the amount of the additive to be added, which naturally affords a big capsule difficult to engulf. Moreover, the protein added per se is unstable to heat and readily forms the Maillard reaction products with concomitant reducing sugars such as lactose, powdered sugar or refined sugar to deteriorate markedly the appearance of the capsules. This method, accordingly, is insufficient.

The object of this invention is to provide hard gelatin capsules resistant to denaturation which are not accompanied by decrease of the solubility or insolubilization time dependently and which release the drug therein steadily.

SUMMARY OF THE INVENTION

The inventors of this invention conducted an extensive study focusing on that peroxidation reaction is one of free radical reaction, and found out that the decrease in hard gelatin capsule solubility and insolubilization is suppressed when a very small amount of a compound with high free radical scavenging activity is added to the capsule content. This invention was accomplished on the basis of these findings.

The gist of this invention is to construct the hard gelatin capsule resistant to denaturation by addition of a free radical scavenger at a rate of 0.01 to 5 weight % to the whole content in said hard gelatin capsule.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 and 2 each shows the drug releasing curve for hard gelatin capsules of Example 2.

Figure 3 shows the drug releasing curve for hard gelatin capsules of Example 4.

DETAILED DESCRIPTION OF THE INVENTION

In the context of this specification, 'free radical scavenger' means anything having free radical scavenging activity (hereinafter referred to as 'RSA'). The mole number of a free radical that can be scavenged by 1 mole of free radical scavenger is referred to as 'RSA value'.

Formulated hard gelatin capsules resistant to denaturation of this invention contain said free radical scavenger and other necessary contents such as drugs and additives in the hard gelatin capsule shells.

The free radical scavenger mentioned above includes anything having a free radical scavenging activity, particularly organic compounds, inorganic compounds and their pharmaceutically acceptable salts having RSA values of not less than 0.01 are preferred. This includes, for example, pharmaceutically acceptable salts of sulfite and hydrogensulfite, as well as cysteine, glutathione, tocopherol, ascorbic acid, thiamine nitrate, riboflavin, β -carotene, acetaminophen, chlorphenilamine maleate, chlorpromazine, pindorol, sesaminol, gossypol, soybean saponine, rosemarinic acid, geraniin, quercetin, glycyrrhyzinic acid, polyphosphoric acid, pyrophosphoric acid, methaphosphoric acid, ferric chloride, etc. and their pharmaceutically acceptable salts. Among them, pharmaceutically acceptable sulfites and hydrogensulfites; and tocopherol, ascorbic acid, polyphosphoric acid, pyrophosphoric acid and their pharmaceutically acceptable salts are preferably used, and moreover, sodium sulfite, sodium hydrogensulfite, tocopherol, pyrophosphoric acid, sodium pyrophosphate and potassium pyrophosphate are particularly preferred.

The preferred amount of said free radical scavenger to be contained is 0.01 to 5 weight % relative to the whole content in the capsules, i.e. the sum of said free radical scavenger and other contents in the capsule. This range is preferred because the amount of not more than 0.01 weight % is not sufficient in avoiding the insolubilization of the gelatin capsule shells, and the amount of over 5 weight % is not effective in increasing the dissolving effect and only results in bulkiness of capsules. Particularly preferred, the amount of the free radical scavenger is 0.01 to 1 weight %.

The other contents mentioned above can be anything except those containing aldehyde as a component. Drugs and additives etc. that are generally employed in formulated capsules can be conveniently employed as well.

Said free radical scavenger and said other component used in this invention may be in any form selected from powder, granules, semisolid, solution and the like. Said granules may be coated with an aqueous coating solution or organic solvent.

According to this invention, said free radical scavenger may be selected in accordance with the combination of drugs and additives; the additives mean excipients, preservatives, disintegrators, coloring agents etc. If desired, one or more kinds of said free radical scavengers can be used in combination.

Said hard gelatin capsule shells mean those commonly used in the art of pharmaceuticals, e.g., Gelatin Capsule III, but are not limited thereto.

The hard gelatin capsules resistant to denaturation of this invention may be produced by conventional methods. For example, said free radical scavenger may be packed into the hard gelatin capsule shells after simply been mixed with the powder or granules of the pharmaceutical composition. Occasionally, said free radical scavenger is incorporated into said granules or their coating layer.

The insolubilization of gelatin capsules is attributable to the following phenomenon: PEG used in aqueous coating or the polyethylene chain of an amphiphatic compound produces peroxidation products such as aldehydes etc., which react with the amino group of gelatin to form a thin film. According to this invention, the free radical generated by time dependent peroxidation of the capsule content during storage under a warmed condition is trapped by the free radical scavenger so that the peroxidation reaction is prevented. Through this process, the generation of aldehyde is suppressed and as a result the formulation of a thin film on the gelatin capsules and insolubilization are inhibited even though PEG and the like are used as fillers.

The effect of this invention is as follows.

According to this invention, time dependent decrease in solubility and insolubilization is prevented to provide a hard gelatin capsules resistant to denaturation having stable drug releasing properties.

EXAMPLES

The following examples further illustrate this invention, however, they do not limit the scope of this invention. All 'parts' in the following examples represents 'weight parts'.

Measurement of RSA values

Each sample was dissolved or dispersed evenly in 0.1M acetic acid buffer (pH 5.5) or methanol. In a stoppered test tube were placed 2 ml of sample solution, 1 ml of 0.6 mM DPPH · methanol solution, and 2 ml of methanol or 0.1M acetic acid buffer (pH 5.5), and the mixture was agitated at room temperature, then centrifuged; the resulting supernatant was collected and the change of absorbance at 530 nm was measured to give the RSA value.

Example 1

In a weighing bottle were placed 95 parts of PEG 6000 and 5 parts of free radical scavengers indicated in table 1, on which a basket containing some empty gelatin capsule III was mounted. The capsule shells and the mixture were stored in a tightly closed glass bottle so that they were kept not to contact each other, at 60°C for a week. Each capsule shell was put in a auxiliary tube for the JP12 disintegration test, then the auxiliary tubes were moved into a glass vessel filled up with about 30 ml of the 2nd solution of JP12 (37 °C) carefully, and after the lapse of 5 to 6 minutes, the solubility was observed. The result is shown in Table 1.

Table 1

Free radical scavenger	Solubility
none	thin film formed, insoluble
ascorbic acid	soluble rapidly
riboflavin	soluble rapidly
d-α -tocopherol	soluble rapidly
thiamine nitrate	soluble rapidly
sodium sulfite	soluble rapidly

According to Example 1, the capsule shells made with PEG 6000 containing no free radical scavenger formed an insoluble thin film; addition of ascorbic acid, riboflavin, tocopherol, thiamine nitrate or sodium sulfite respectively, completely prevented the decrease of the solubility of the capsule shells.

Example 2

Coated granules (herein after referred to as 'Mixture A') were prepared by mixing 30.0 mg of cristalline cellulose, 10.0 mg of pyridoxine hydrochloride, 54.0 mg of lactose, 5.0 mg of corn starch, 31.5 mg of talc, 0.3 mg of aerosil, 1.2 mg of magnesium stearate, 7.7 mg of triethyl citrate, 0.5 mg of HPC-L, and 38.3 mg of HPMC-AS, and a variety of compounds indicated in Table 2 were added to Mixture A to give the compositions which were packed into a gelatin capsule III. After having been stored in a tightly closed glass bottle at 60 °C for 5 days, the releasing test was conducted. The releasing test was effected according to the Paddle method of the Japanese Pharmacopoeia (paddle speed: 100

rpm), using 900 ml of the 2nd solution of JP 12 as releasing solution. The results are shown in Figures 1 and 2.

Table 2

Compound	Mixing amount (mg)								
	Comparative formulation A	Comparative formulation B	Comparative formulation C	Comparative formulation D	Formulation E	Formulation F	Formulation G	Formulation H	Formulation I
Mixture A	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5
Sodium dihydrogenphosphate	—	0.7	—	—	—	—	—	—	—
Ethenzamide	—	—	0.7	—	—	—	—	—	—
Aspirin	—	—	—	0.7	—	—	—	—	—
Acetaminophen	—	—	—	—	0.7	—	—	—	—
Cysteine	—	—	—	—	—	0.7	—	—	—
Sodium pyrophosphate	—	—	—	—	—	—	0.7	—	—
Sodium sulfite	—	—	—	—	—	—	—	0.5	—
Sodium hydrogensulfite	—	—	—	—	—	—	—	—	0.5
Total	178.5	179.2	179.2	179.2	179.2	179.2	179.2	179.0	179.0

According to Example 2, Comparative formulation A with only Mixture A, and Comparative formulations B, C and D containing sodium hydrogenphosphate, ethenzamide and aspirin, respectively, have no scavenging effect, resulting in insolubilization of the capsules and reducing their drug releasing ability after storage with heat. On the other hand,

Formulations E, F, G, H and I containing acetaminophen, cysteine, sodium pyrophosphate, sodium sulfite, and sodium hydrogensulfite, respectively, having great RSA values, did not cause insolubilization of the capsules, and no reduction of the drug releasing ability was observed.

Example 3

Five parts of each free radical scavenger indicated in Table 3 and 95 parts of PEG 4000 were admixed in a mortar, and packed into gelatin capsule III. After storage in a tightly closed glass bottle at 60°C for a week, the capsule content was removed and solubility of each capsule shell was examined in the same manner as in Example 1. The result is shown in Table 3.

Table 3

Free radical scavenger	Solubility
none	thin film formed, insoluble
d-α -tocopherol	soluble rapidly
polyphosphoric acid	soluble rapidly
methaphosphoric acid	soluble rapidly
glutathione	soluble rapidly

According to Example 3, when no free radical scavenger was added, the capsules formed a thin film inducing insolubilization. On the other hand, when the free radical scavenger was added, no decrease in solubility of the capsules was observed after storage under warm conditions.

Example 4

Ten parts of ethenzamide, and 5 parts of each tocopherol, cysteine, or sodium sulfite were dissolved in 50 parts of Tween 80 (trade name) and 35 parts of Span 20 (trade name). The mixture was packed into gelatin capsule shells, stored in a tightly closed glass bottle at 60°C for a week. The releasing test was effected in the same manner as in Example 2. The result is shown in Figure 3.

According to Example 4, while no addition of tocopherol or other free radical scavengers caused insolubilization of the capsules and decrease in drug releasing ability were observed, when added these scavengers, no insolubilization and decrease in drug releasing ability was observed.

Claims

1. A formulated hard gelatin capsule resistant to denaturation which contains a free radical scavenger at a rate of 0.01 to 5 weight % for the whole content.

2. The formulated hard gelatin capsule resistant to denaturation according to Claim 1, wherein the content of said free radical scavenger is 0.01 to 1 weight % for the whole content.

3. The formulated hard gelatin capsule resistant to denaturation according to Claim 1 or 2, wherein said free radical scavenger is one or more selected from the group consisting of pharmaceutically acceptable sulfites, pharmaceutically acceptable hydrogensulfites, and, tocopherol, ascorbic acid, polyphosphoric acid, pyrophosphoric acid, and the pharmaceutically acceptable salts thereof.

4. The formulated hard gelatin capsule resistant to denaturation according to Claim 3, wherein said free radical scavenger is sodium sulfite, sodium hydrogensulfite, sodium pyrophosphate and/or potassium pyrophosphate.

5. The formulated hard gelatin capsule resistant to denaturation according to any one of claims 1 to 4 additionally containing at least one pharmaceutically active compound.

6. A method for producing formulated hard gelatin capsules resistant to denaturation, wherein a free radical scavenger is added to the capsules at a rate of 0.01 to 5 weight % for the whole content.

7. The method for producing a formulated hard gelatin capsule resistant to denacuration according to Claim 6, wherein the content of said free radical scavenger is 0.01 to 1 weight % for the whole content.

8. Use of a formulated hard gelatin capsule resistant to denaturation according to claim 5 as a sustained release preparation.

9. Use of a free radical scavenger to prevent the decrease of solubility of a hard gelatin capsule during storage.

Figure 1

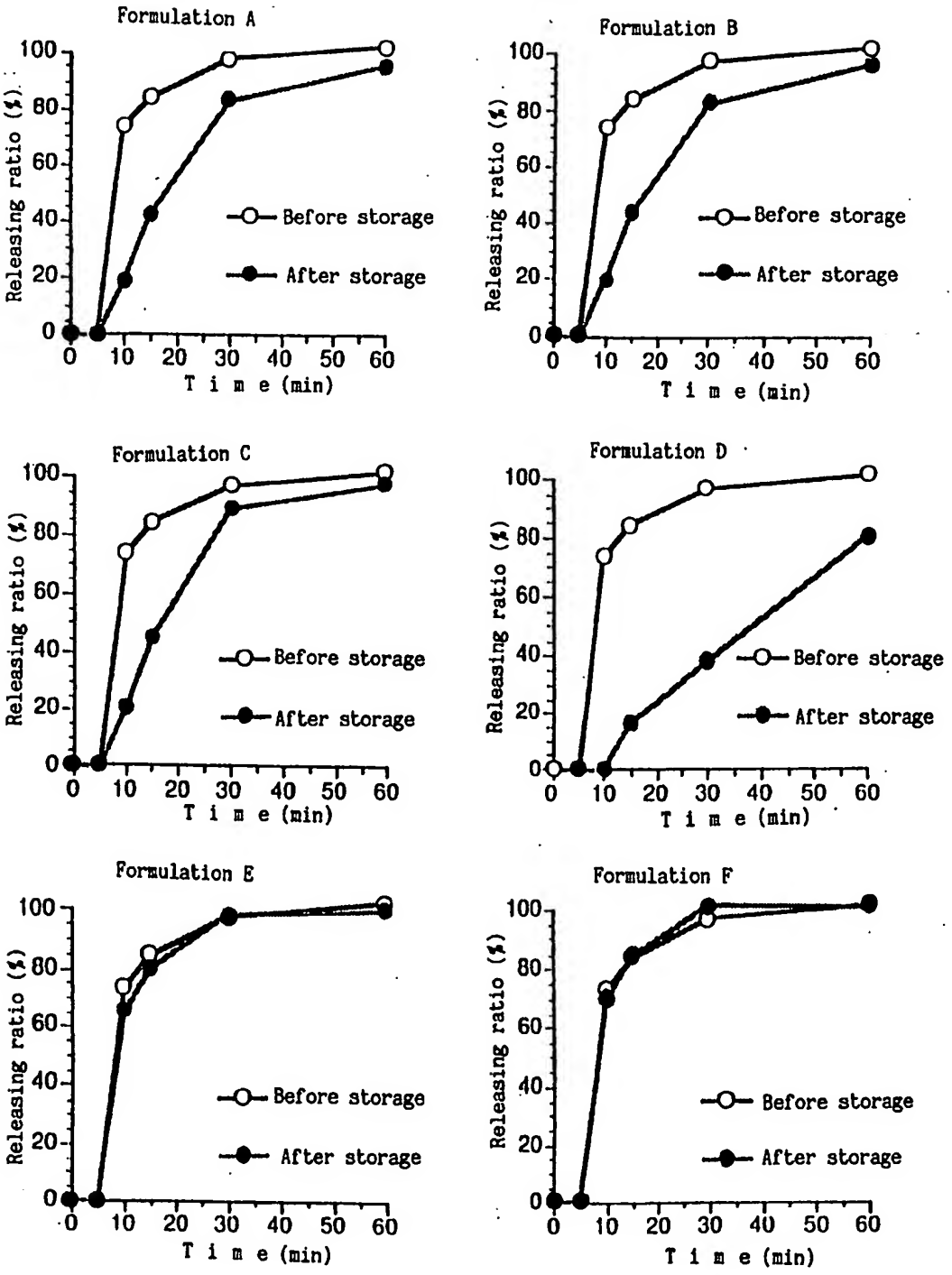

Formulation A
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation B
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation C
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation D
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation E
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation F
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage

Figure 2

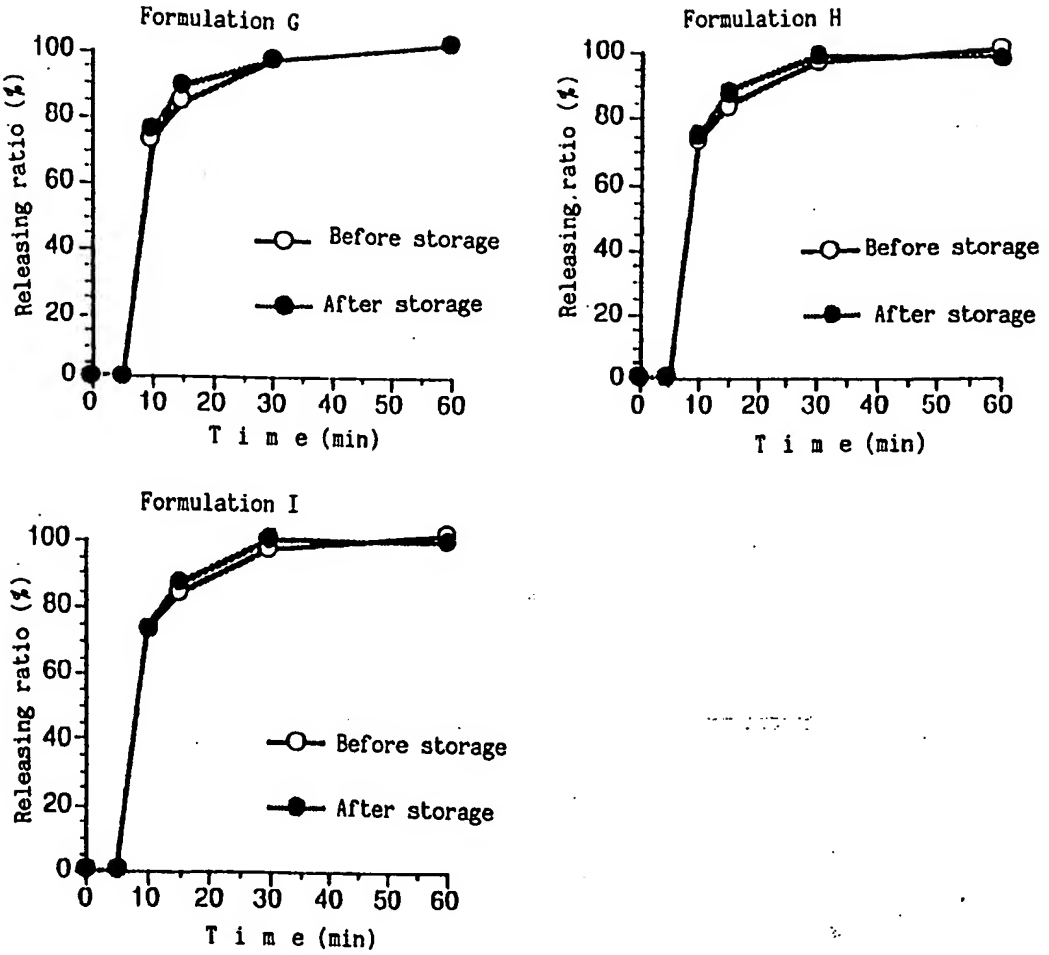
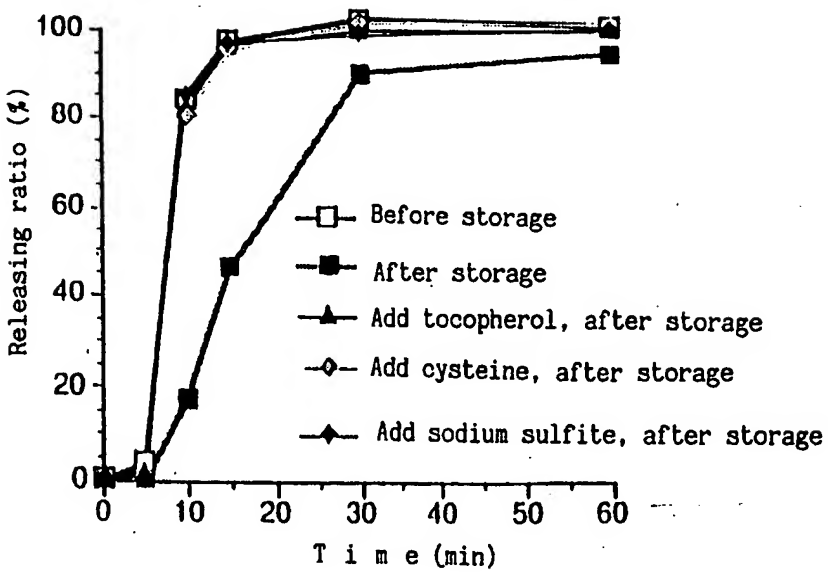

Formulation G
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation H
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage
Formulation I
Releasing ratio (%)
100
80
60
40
20
0
0 10 20 30 40 50 60
T i m e (min)
Before storage
After storage

Figure 3


100
80
60
40
20
0
Releasing ratio (%)
0
10
20
30
40
50
60
T i m e (min)
Before storage
After storage
Add tocopherol, after storage
Add cysteine, after storage
Add sodium sulfite, after storage

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 11 2088

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	FR-A-2 617 047 (SANOFI ET AL) * claims 1-10 * * page 2, line 23 - page 3, line 3 * ---	1-9	A61K9/48
X D	FR-A-2 204 401 (MEIJI SEIKA CO. LTD.) * claims 1-12 * * page 2, line 10 - line 13 * * example 4 * & JP-B-51 015 094 ---	1-9	
A	JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 83, no. 7, July 1994 WASHINGTON, DC, US, pages 915-921, G. A. DIGENIS ET AL 'Cross-Linking of Gelatin Capsules and Its Relevance to Their in Vitro-in Vivo Performance' * page 917 - page 919, left column * -----	1-9	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	17 November 1995	Siatou, E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Hard gelatin capsules resistant to denaturation and the production thereof

Claims of corresponding document: **EP0695544**

1. A formulated hard gelatin capsule resistant to denaturation which contains a free radical scavenger at a rate of 0.01 to 5 weight % for the whole content.

2. The formulated hard gelatin capsule resistant to denaturation according to Claim 1, wherein the content of said free radical scavenger is 0.01 to 1 weight % for the whole content.

3. The formulated hard gelatin capsule resistant to denaturation according to Claim 1 or 2, wherein said free radical scavenger is one or more selected from the group consisting of pharmaceutically acceptable sulfites, pharmaceutically acceptable hydrogensulfites, and, tocopherol, ascorbic acid, polyphosphoric acid, pyrophosphoric acid, and the pharmaceutically acceptable salts thereof.

4.The formulated hard gelatin capsule resistant to denaturation according to Claim 3, wherein said free radical scavenger is sodium sulfite, sodium hydrogensulfite, sodium pyrophosphate and/or potassium pyrophosphate.

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8. Use of a formulated hard gelatin capsule resistant to denaturation according to claim 5 as a sustained release preparation.

9. Use of a free radical scavenger to prevent the decrease of solubility of a hard gelatin capsule during storage.

Hard gelatin capsules resistant to denaturation and the production thereof

Description of corresponding document: **EP0695544**

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For example, it is usual that a granulated drug is coated with an aqueous coating solution of enteric polymer or water-insoluble polymer and packed in hard gelatin capsules in order to minimize the difference in the rate of intestinal drug absorption among persons which depends on the velocity of drug movement in the gastrointestinal tract. Moreover, the formulation by hard gelatin capsules is also utilized to avoid the damage of appearance of drugs, which is sometimes accompanied by the addition of amphiphilic compounds, e.g., Tween (trade name), Span (trade name), polyethylene glycol (PEG), which are added to improve the wettable property of sparingly soluble drugs.

In the above cases, however, the hard gelatin capsules are sometimes denatured during storage under a warmed condition and the drug release is greatly inhibited since the capsules contain aqueous-coating granular drugs or amphiphilic compounds with polyoxyethylene chains.

The reason may be attributable to that PEG, triethyl citrate, etc. used as plasticizer in aqueous coating or the polyoxyethylene chain of the amphiphilic compounds is thermally decomposed to yield peroxidation products such as aldehydes, which act to induce intramolecular or intermolecular bridge formation or polymerization in gelatin.

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Applicant: SHIONOGI & CO (JP)
Classification:
- international: ***A61K9/48;*** **A61K9/48**; (IPC1-7): A61K9/48
- european: A61K9/48H4
Application number: DE19956019340T 19950801
Priority number(s): JP19940204322 19940805

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EP0695544 (B1)

Abstract not available for DE69519340T
Abstract of corresponding document: **EP0695544**

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The preferred amount of said free radical scavenger to be contained is 0.01 to 5 weight % relative to the whole content in the capsules, i.e. the sum of said free radical scavenger and other contents in the capsule. This range is preferred because the amount of not more than 0.01 weight % is not sufficient in avoiding the insolubilization of the gelatin capsule shells, and the amount of over 5 weight % is not effective in increasing the dissolving effect and only results in bulkiness of capsules. Particularly preferred, the amount of the free radical scavenger is 0.01 to 1 weight %.

The other contents mentioned above can be anything except those containing aldehyde as a component. Drugs and additives etc. that are generally employed in formulated capsules can be conveniently employed as well.

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Said hard gelatin capsule shells mean those commonly used in the art of pharmaceuticals, e.g., Gelatin Capsule III, but are not limited thereto.

The hard gelatin capsules resistant to denaturation of this invention may be produced by conventional methods. For example, said free radical scavenger may be packed into the hard gelatin capsule shells after simply been mixed with the powder or granules of the pharmaceutical composition. Occasionally, said free radical scavenger is incorporated into said granules or their coating layer.

The insolubilization of gelatin capsules is attributable to the following phenomenon: PEG used in aqueous coating or the polyethylene chain of an amphiphatic compound produces peroxidation products such as aldehydes etc., which react with the amino group of gelatin to form a thin film. According to this invention, the free radical generated by time dependent peroxidation of the capsule content during storage under a warmed condition is trapped by the free radical scavenger so that the peroxidation reaction is prevented. Through this process, the generation of aldehyde is suppressed and as a result the formulation of a thin film on the gelatin capsules and insolubilization are inhibited even though PEG and the like are used as fillers.

The effect of this invention is as follows.

According to this invention, time dependent decrease in solubility and insolubilization is prevented to provide a hard gelatin capsules resistant to denaturation having stable drug releasing properties.

EXAMPLES

The following examples further illustrate this invention, however, they do not limit the scope of this invention. All 'parts' in the following examples represents 'weight parts'.

Measurement of RSA values

Each sample was dissolved or dispersed evenly in 0.1M acetic acid buffer (pH 5.5) or methanol. In a stoppered test tube were placed 2 ml of sample solution, 1 ml of 0.6 mM DPPH . methanol solution, and 2 ml of methanol or 0.1M acetic acid buffer (pH 5.5), and the mixture was agitated at room temperature, then centrifuged; the resulting supernatant was collected and the change of absorbance at 530 nm was measured to give the RSA value.

Example 1

In a weighing bottle were placed 95 parts of PEG 6000 and 5 parts of free radical scavengers indicated in table 1; on which a basket containing some empty gelatin capsule III was mounted. The capsule shells and the mixture were stored in a tightly closed glass bottle so that they were kept not to contact each other, at 60 DEG C for a week. Each capsule shell was put in a auxiliary tube for the JP12 disintegration test, then the auxiliary tubes were moved into a glass vessel filled up with about 30 ml of the 2nd solution of JP12 (37 DEG C) carefully, and after the lapse of 5 to 6 minutes, the solubility was observed.The result is shown in Table 1.
<tb><TABLE> Id=Table 1 Columns=2
<tb>
<tb>Head Col 1: Free radical scavenger
<tb>Head Col 2: Solubility
<tb>none<SEP>thin film formed, insoluble
<tb>ascorbic acid<SEP>soluble rapidly
<tb>riboflavin<SEP>soluble rapidly
<tb>d- alpha -tocopherol<SEP>soluble rapidly
<tb>thiamine nitrate<SEP>soluble rapidly
<tb>sodium sulfite<SEP>soluble rapidly

<tb></TABLE>

According to Example 1, the capsule shells made with PEG 6000 containing no free radical scavenger formed an insoluble thin film; addition of ascorbic acid, riboflavin, tocopherol, thiamine nitrate or sodium sulfite respectively, completely prevented the decrease of the solubility of the capsule shells.

Example 2

Coated granules (herein after referred to as 'Mixture A') were prepared by mixing 30.0 mg of cristalline cellulose, 10.0 mg of pyridoxine hydrochloride, 54.0 mg of lactose, 5.0 mg of corn starch, 31.5 mg of talc, 0.3 mg of aerosil, 1.2 mg of magnesium stearate, 7.7 mg of triethyl citrate, 0.5 mg of HPC-L, and 38.3 mg of HPMC-AS, and a variety of compounds indicated in Table 2 were added to Mixture A to give the compositions which were packed into a gelatin capsule III. After having been stored in a tightly closed glass bottle at 60 DEG C for 5 days, the releasing test was conducted. The releasing test was effected according to the Paddle method of the Japanese Pharmacopoeia (paddle speed: 100 rpm), using 900 ml of the 2nd solution of JP 12 as releasing solution. The results are shown in Figures 1 and 2.
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According to Example 2, Comparative formulation A with only Mixture A, and Comparative formulations B, C and D containing sodium hydrogenphosphate, ethenzamide and aspirin, respectively, have no scavenging effect, resulting in insolubilization of the capsules and reducing their drug releasing ability after storage with heat. On the other hand, Formulations E, F, G, H and I containing acetaminophen, cysteine, sodium pyrophosphate, sodium sulfite, and sodium hydrogensulfite, respectively, having great RSA values, did not cause insolubilization of the capsules, and no reduction of the drug releasing ability was observed.

Example 3

Five parts of each free radical scavenger indicated in Table 3 and 95 parts of PEG 4000 were admixed in a mortar, and packed into gelatin capsule III. After storage in a tightly closed glass bottle at 60 DEG C for a week, the capsule content was removed and solubility of each capsule shell was examined in the same manner as in Example 1. The result is shown in Table 3.
<tb><TABLE> Id=Table 3 Columns=2
<tb>
<tb>Head Col 1: Free radical scavenger
<tb>Head Col 2: Solubility
<tb>none<SEP>thin film formed, insoluble
<tb>d- alpha -tocopherol<SEP>soluble rapidly
<tb>polyphosphoric acid<SEP>soluble rapidly
<tb>methaphosphoric acid<SEP>soluble rapidly
<tb>glutathione<SEP>soluble rapidly
<tb></TABLE>

According to Example 3, when no free radical scavenger was added, the capsules formed a thin film inducing insolubilization. On the other hand, when the free radical scavenger was added, no decrease in solubility of the capsules was observed after storage under warm conditions.

Example 4

Ten parts of ethenzamide, and 5 parts of each tocopherol, cysteine, or sodium sulfite were dissolved in 50 parts of Tween 80 (trade name) and 35 parts of Span 20 (trade name). The mixture was packed into gelatin capsule shells, stored in a tightly closed glass bottle at 60 DEG C for a week. The releasing test was effected in the same manner as in Example 2. The result is shown in Figure 3.

According to Example 4, while no addition of tocopherol or other free radical scavengers caused insolubilization of the capsules and decrease in drug releasing ability were observed, when added these scavengers, no insolubilization and decrease in drug releasing ability was observed.

Family list
13 family members for:
JP8099869
Derived from 10 applications.

Back to JP8

1 **GEGEN DENATURIERUNG BESTÄNDIGE HARTGELATINE- KAPSELN UND VERFAHREN ZU IHRER HERSTELLUNG**
Publication info: **AT197399T T** - 2000-11-11

2 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **CN1086941C C** - 2002-07-03
CN1124619 A - 1996-06-19

3 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **DE69519340D D1** - 2000-12-14

4 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **DE69519340T T2** - 2001-06-21

5 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **DK695544T T3** - 2001-01-02

6 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **EP0695544 A1** - 1996-02-07
EP0695544 B1 - 2000-11-08

7 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **ES2151940T T3** - 2001-01-16

8 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **GR3035264T T3** - 2001-04-30

9 **SOFT GELATIN CAPSULE PREVENTED FROM DETERIORATING AND ITS PRODUCTION**
Publication info: **JP3557008B2 B2** - 2004-08-25
JP8099869 A - 1996-04-16

10 **Hard gelatin capsules resistant to denaturation and the production thereof**
Publication info: **PT695544T T** - 2001-03-30

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